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(54) Title: BISPHOSPHONATE CEMENT COMPOSITION TO PREVENT ASEPTIC LOOSENING OF ORTHOPEDIC IMPLANT DEVICES

(57) Abstract

Disclosed is a bisphosphonate bone cement for preventing periprosthetic bone loss and aseptic loosening of a joint prosthesis in patients, which cement contains a bisphosphonate bone resorption inhibitor, e.g., sodium or calcium salt of alendronate, and a pharmaceutically acceptable polymeric carrier such as polymethylmethacrylate.

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TITLE OF THE INVENTION

BISPHOSPHONATE CEMENT COMPOSITION TO PREVENT ASEPTIC LOOSENING OF ORTHOPEDIC IMPLANT DEVICES

FIELD OF THE INVENTION

The instant invention relates to the use of bisphosphonate salts, e.g., alendronate, in an acrylate-based polymer bone cement such as polymethylmethacrylate (PMMA), to prevent periprosthetic bone loss and failure of a joint prosthesis and in arthroplasty patients having an orthopedic implant device.

BACKGROUND OF THE INVENTION

There are approximately 300,000 prosthetic implants performed per year on a world-wide basis, including hip and knee implants. Of this population, there is about a 5-50% failure rate within ten years of the operation, depending upon the specific type of prosthesis, requiring a repeat surgery and device re-implant. This failure rate increases exponentially with time so that many patients with an aging prosthesis gradually experience pain at the site of the implant and eventually require implant replacement. This condition of pain is considered to be a result of fragmentation of the cement substances utilized in hip prostheses, leading to macrophage-mediated inflammation. Further, at the time these patients develop pain and loosening of the joint, they also exhibit markedly increased bone turnover, especially bone resorption, in the periprosthetic bone immediately adjacent to the implant. Evidence for this bone turnover can be seen from the fact that bone scanning agents, which include bisphosphonates tagged with technetium, are often taken up at very high concentrations in these areas of the periprosthetic bone. Bone turnover in this instance, unfortunately, leads to a steady loss of the supporting periprosthetic bone structure, aseptic (absence of bacterial infection) loosening of the implant device and making necessary replacement surgery. See *J. Bone and Joint Surgery*, Vol.

74-A, No. 6, pages 849-862 (July 1992) and Vol 75-A, No. 6 pages 802-813 (June 1993).

Applicants have discovered that this problem can be overcome by incorporating a bone resorption inhibitor into the implant cement, which binds (fixates) the device to the supporting trabecular or cortical bone in the cavity in which the bone is inserted. The presence of a bone resorption inhibitor should sufficiently inhibit bone resorption in the periprosthetic area of the implant device to obviate replacement surgery.

Most of the currently new bone resorption inhibitors are non-estrogenic therapeutic agents in the class of bisphosphonates. These compounds are used in the treatment of osteoporosis, and act by reducing and/or inhibiting bone resorption in the osteoporotic patient. The following are examples in the art of bisphosphonates currently being studied:

US Patent No. 4,621,077, issued Nov. 4, 1986 to Rosini and Staibano discloses pharmaceutical compositions comprising (4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid (ABP) or a water-soluble (sodium, aniline or lysine) salt thereof.

Alendronate, 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium trihydrate is a known bone resorption inhibitor and is described in U.S. Patents 4,922,007 and 5,019,651 (Merck).

Clodronate, (dichloromethylene)bisphosphonic acid disodium salt (Proctor and Gamble, is described in Belgium Patent 672,205 (1966) and its preparation is found in *J. Org. Chem 32*, 4111 (1967).

Tiludronate, ([(4-chlorophenyl)thiomethylene]-bisphosphonic acid) (Sanofi) is described in U.S. Patent 4,876,248 issued October 24, 1989.

YM 175 ([(cycloheptylamino)methylene]bisphosphonic acid, disodium salt) by Yamanouchi is described in U.S. Patent 4,970,335 issued November 13, 1990.

CGP 42'446, being 2-(imidazol-1-yl)-hydroxyethyl-idene-1,1-bisphosphonic acid is a Ciba Geigy compound and is described in Bone and Mineral, Abstracts, Supplement 1 to Vol 25, April 1994, S61, Article 12, by A. Pataki *et al.*

Ibandronate, BM 21.0995 (1-Hydroxy-3-(methylpentyl-amino)-propylidene-bisphosphonate) by Boehringer-Mannheim - is described in U.S. Patent 4,927,814 issued May 22, 1990.

A study by Proctor and Gamble (Norwich Eaton Pharmaceuticals) using risedronate, whose chemical name is sodium trihydrogen [1-hydroxy-2-(3-pyridinyl)ethylidene]bisphosphonate, in combination with estrogen showed a positive effect of both of these agents to prevent or reverse bone loss in ovariectomized rats (published in Abstracts 731 and 732 at the Fall 1992 ASBMR meeting in Minnesota).

The article, "*J. Clin. Invest.*", Jan. 1992, *89* (1), p. 74-78 by J. Chow *et al.*, describes a study on ovariectomized rats in which bone resorption was suppressed by pamidronate whose chemical name is 3-amino-1-hydroxy propylidene-bisphosphonic acid disodium salt. They concluded that pamidronate inhibits bone resorption.

Mildronate, a derivative of pamidronate, 3-(N,N-dimethyl)amino-1-hydroxy-propylidene-bisphosphonic acid, dimethyl-APD, is described in Bone and Mineral, Abstracts, Supplement 1 to Vol 25, April 1994, S79, Article 78, by D. González *et al.*

Another Proctor and Gamble compound, piridronate, [2-(2-pyridinyl)ethylidene]-bisphosphonic acid, monosodium salt is described in USP 4,761,406 as having bone resorption inhibition activity.

Quaternary nitrogen derivatives of piridronate, including NE-58051, NE-58095, NE-58043, NE-10244, NE-1-0446 are described in Bone and Mineral, Abstracts, Supplement 1 to Vol 25, April 1994, S65, Article 24, by F. H.Ebetino *et al.*

The article, "Monatschefte" *99*, 2016 (1968) by F. Kasparet describes the synthesis of etidronate, (1-hydroxy-ethylidene)bisphosphonic acid, disodium salt, (Proctor and Gamble).

The above bisphosphonates are readily water soluble. For extended bioavailability in the area of the periprosthetic bone, water-insoluble bisphosphonate salts, e.g., calcium salts, would also be desired for formulating a cement.

US Patent No. 4,446,052, issued May 1, 1984 to Sunberg and Benedict, discloses a gel comprising di[(3-amino-1-hydroxy-propylidene)-1,1-bisphosphonic acid]tricalcium salt in water. The gel is disclosed to be useful for the treatment of certain disorders of calcium metabolism in warm blooded animals.

US Patent 5,356,887, issued October 18, 1994 to Brenner *et al.* and assigned to Merck & Co., Inc., discloses three new insoluble calcium salts of alendronate: [(4-amino-1-hydroxy-butylidene)-1,1-bisphosphonic acid]monocalcium salt, (ABP)Ca; di[(4-amino-1-hydroxybutylidene)-1,1-bisphosphonic acid]mono-calcium salt, $(ABP)_2Ca$; and tri[(4-amino-1-hydroxybutylidene)-1,1-bisphosphonic acid]tetracalcium salt, $(ABP)_3Ca_4$. These salts are described as useful in intramuscular or subcutaneous injection.

However, the above cited art does not suggest or describe the use of a bisphosphonate being incorporated into a polymethyl-methacrylate bone implant cement to specifically prevent aseptic loosening and bone resorption in the periprosthetic bone area of an orthopedic implant device.

What is desired in the art is a bone implant cement to optimally prevent excessive bone resorption in the periprosthetic area of an implant device, i.e., the bone area which is in contact and close proximity to the cement surface, to retard the aseptic loosening and failure of the device and thereby to prevent the pain, morbidity and cost associated with this condition.

SUMMARY OF THE INVENTION

We have discovered that a bisphosphonate salt can be used in a bone fixation cement for patients for the prevention of failure of joint prostheses, e.g., for the hip or knee. Administration of a fixation cement containing a bisphosphonate, e.g., alendronate, can provide extended therapeutic action and prevent the periprosthetic bone resorption process and thereby maintain the integrity of the total prosthetic structure.

By this invention there is provided a bone implant cement comprising a pharmaceutically acceptable polymeric carrier and an effective amount of a bisphosphonate bone resorption inhibitor.

The bisphosphonate applicable in the cement includes the free acids, and pharmaceutically acceptable salts, e.g., sodium, potassium, ammonium, calcium, magnesium and barium salts of: alendronate, clodronate, tiludronate, YM 175, ibandronate (BM 21.0995), risedronate, piridronate, pamidronate, or combinations thereof.

Further provided is a method of preventing failure of a joint prosthesis implanted into a bone cavity in the presence of an orthopedic bone cement in a patient comprising the steps of:

(a) adding a bisphosphonate to the orthopedic bone cement;

(b) adding the cement from step (a) to the bone cavity;

(c) implanting the joint prosthesis into the bone cavity.

DETAILED DESCRIPTION OF THE INVENTION AND PREFERRED EMBODIMENTS

The bisphosphonates described above are useful in the invention cement. Very useful are the sodium, potassium and calcium salts of residronate, clodronate, tiludronate and alendronate and particularly useful are the sodium and calcium salts of alendronate, i.e., monosodium alendronate trihydrate, disodium

alendronate, anhydrous monosodium alendronate, di[(3-amino-1-hydroxypropylidene)-1,1-bisphosphonic acid]tricalcium, [(4-amino-1-hydroxybutylidene)-1,1-bisphosphonic acid]monocalcium salt, (ABP)Ca, di[(4-amino-1-hydroxybutylidene)-1,1-bisphosphonic acid]monocalcium salt, $(ABP)_2Ca$, and tri[(4-amino-1-hydroxybutylidene)-1,1-bisphosphonic acid]tetracalcium salt, $(ABP)_3Ca_4$.

The cement disclosed herein can be used to treat human subjects at the time of insertion of a prosthesis, i.e., a medical implant device.

The method described herein involves the administration of a bisphosphonate fixation cement in an osteogenically effective amount to inhibit bone resorption in the periprosthetic bone area of a medical implant device.

By the term "periprosthetic bone area" as used herein is meant the area of bone which is in contact with the medical implant device, including the cement, or in the immediate proximity thereof.

By the term "sodium alendronate" as used herein, is meant alendronate, being 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium trihydrate.

By the term "calcium alendronate" as used herein, is meant the above four listed insoluble calcium salts.

Very useful bisphosphonates salt in the invention are alendronate and calcium alendronate.

By the term "insoluble" as used herein, is meant that the aqueous solubility of the bisphosphonate, calcium alendronate, at room temperature is not appreciable.

The term "inhibition of bone resorption" as used herein refers to prevention of bone loss, especially the inhibition of removal of existing bone either from the mineral phase and/or the organic matrix phase, through direct or indirect alteration of osteoclast formation or activity. Thus, the term "inhibitor of bone resorption" as used herein refers to agents that prevent bone loss by the direct or indirect alteration of osteoclast formation or activity.

The term "osteogenically effective" as used herein means that amount which decreases the turnover of mature bone. As used herein, an osteogenically effective dose is also "pharmaceutically effective."

The term "subject" as used herein refers to a living vertebrate animal such as a mammal in need of treatment, i.e., in need of an implant device

The term "preventing" as used herein shall mean providing a subject with an amount of a bisphosphonate in a bone cement sufficient to act prophylactically on the bone cavity and the periprosthetic bone area to prevent the loosening of the implant device.

By the term "cement", as used herein, is meant to encompass the mixed cement composition containing all of the ingredients and components prior to, during, and after complete "curing", i.e., during early stages of monomer polymerization, at partial polymerization and complete polymerization. Thus, the term "cement" can include the kneaded precured mass containing unpolymerized methylmethacrylate just prior to insertion into the bone cavity, the inserted mass just after insertion, and the fully polymerized cement , i.e., "fully cured", inside the bone cavity in contact with the prosthetic bone and the implant device after sufficient time for complete curing, e.g., 15-20 minutes.

In general, conventional bone cements currently used in arthroplastic procedures are FDA approved "cold" self-curing polymethylmethacrylate (PMMA)-based compositions which cure at room temperature or body temperature.

Generally bone cements have to be prepared immediately prior to using and and consist of two parts: first, a solid acrylate polymer part, which is generally a sterile package containing fully polymerized polymer, e.g., PMMA beads of substantially uniform small particle size of about 5-20 microns average diameter, and a catalyst, e.g., a solid aromatic peroxide such as benzoyl peroxide, present in about in one weight percent or less; and a second

part, containing the acrylate monomer, which is generally a sterilized ampoule containing the acrylate or methacrylate monomer, e.g., methylmethacrylate, and an initiator, e.g., an N,N-disubstituted aromatic amine such as N,N-dimethyl-p-toluidine, present in about one weight percent or less. The second part can also contain a small quantity of a monomer stabilizer e.g., hydroquinone or a dicarboxylic acid, such as ascorbic acid in about 0.02 weight percent or less of the composition. A small amount of ethyl alcohol in about one weight percent or less can also be present to help solubilize the ascorbic acid. When the initiator comes into contact with the catalyst upon mixing of the polymer powder and monomer parts, the activator-catalyst interaction activates the catalyst to initiate the polymerization of the monomer.

The polymer powder part can also contain a radiopaquing agent, e.g., zirconium oxide or barium sulfate, present in about 5-15 weight percent of the composition, to distinguish the cement from bone during subsequent X-ray analysis and monitoring of the implanted device.

Both the polymer powder and monomer parts can also contain a non-toxic pigmented coloring agent e.g., chlorophyll, present in less than 0.1 weight percent, to enable easy identification in the surgical room during handling and preparation.

Further, an antibiotic can be included in the polymer powder part, e.g., gentamicin sulfate, or tetracycline, present in about 1-2 weight percent or less, to prevent bacterial infection in the periprosthetic area.

The separately packaged polymer powder can be sterilized prior to use with, e.g., gamma radiation; the monomer can be sterilized by e.g., sterile microfiltration; and the package containing the polymer part can be sterilized by e.g., ethylene oxide.

In practice, the contents of the polymer powder and monomer parts are mixed in an area having an exhaust system in the surgical room just prior to application. All sterile instruments are used in the mixing procedure. The monomer is added to the

polymer powder during mixing at room temperature being careful not to entrap air and create air voids. Care must be taken in handling the monomer since it is volatile and flammable. The polymerization of the monomer begins which binds together the polymer producing a dough-like mass over a 1-2 minute period. The mass is kneaded to a desirable consistency and then placed into the bone cavity, which has been previously washed with cold saline soution and dried, under a slight pressure, by sterile gloved hand, sterile spatula, or by a syringe applicator to force the cement into the spongy areas of the bone to eliminate "air pockets" between the bone cavity and the cement. The reason for this is that the cement is not an adhesive and depends upon mechanical interlock of bone, cement and implant surfaces for good fixation. The implant device is then firmly inserted into the bone cavity and the excess cement removed. The implant is held firmly in place until complete curing occurs in about a 7-8 minute period. The rest of the arthroplastic structure is then assembled.

The cement useful herein contains a bisphosphonate admixed with a polymeric base.

Representative examples of polymers that can be used as the polymeric base for fixation of bone implants are polyacrylic acid ester and polymethylacrylic acid ester types, e.g., polymethacrylate and polymethylmethacrylate, including copolymers of polyacrylic acid ester/polymethacrylic acid ester, and copolymers with polyalkyl-methylmethacrylate. Specific polymers include: polyalkylmethacrylates including polymethylmethacrylate (PMMA) and polyethylmethacrylate, polymethacrylate, polymethylmeth-acrylate/polymethacrylate copolymers, copolymers of methyl-methacrylate including methylmethacrylate/n-decylmeth-acrylate/isobornylmethacrylate, copolymers and mixtures thereof the above polymers, and the like. A very useful polymer is polymethylmethacrylate.

The dosage or amount of bisphosphonate in the cement necessary to achieve therapeutic effectiveness, will vary with the age, size, sex and condition of the subject, the nature and severity of the disorder to be treated, and the like; thus, a precise effective amount is best determined by the caregiver. In general terms, an effective amount of biphosphonate is about 0.005 to 10 weight percent of the total cement composition and a particularly useful range is 0.1 to 2 weight percent.

The method of the invention is useful for preventing defects and disorders in the periprosthetic area of the joint prosthesis which can result in a weakened or loosened structure and/or pain.

The bisphosphonate-containing cement may be implanted directly at the site to be treated, for example, by injection or surgical implantation.

Bisphosphonate delivered in cement is useful for maintaining implant fixation, by preventing or delaying the onset of aseptic loosening.

Preparations of the bisphosphonates, disodium alendronate and anhydrous monosodium alendronate, which are operable in the cement, are shown below.

SUPPORTING EXAMPLE I

4-Amino-1-Hydroxy-Butylidene-1,1-Bisphosphonic Acid Disodium Salt Monohydrate

To a suspension of 4-amino-1-hydroxy-1,1-diphosphonic acid (3.97 g) in 150 ml of distilled water was added with stirring aqueous sodium hydroxide (0.5N) until the pH of the soution was 9.2. The stirred solution was triturated with 200 ml ethanol (absolute) to give a suspension of a fine white solid which was chilled at 5 degrees C. overnight. The obtained solid was collected by vacuum filtration, air dried, and then dried *in vacuo* at 100 degrees C. at 0.2 torr for 18 hours over P_2O_5 to yield 4.38 g, (88%) yield of the disodium salt

monohydrate title compound. A sample was submitted for CHN analysis;

For $C_4H_{11}NO_4P_2Na_2:H_2O$:

Anal.: C, 15.44; H, 4.21; N, 4.50

Found: C, 15.28; H, 4.49; N, 4.49

Melting Point of the solid was above 300 degrees C.

Solubility of the disodium salt in water is about 200mg/ml as compared to the free acid which is 8 mg/ml.

The solution pH of the disodium salt at 50 mg/ml. is 8.7, as compared to the free acid which is pH 2.2 at 8 mg/ml.

SUPPORTING EXAMPLE II

Interconversion of Hydrated Forms of Disodium Salt

The above obtained monohydrate from Example 1 is exposed to a relative humidity atmosphere at 76% at room temperature for 24-48 hours resulting in the pentahydrate salt.

Exposure of this pentahydrate salt to 0% relative humidity at room temperature for 24-48 hours results in a trihydrate salt.

The trihydrate salt is heated to 100 degrees C. for 1-4 hours and results in a 2.5 hydrate (hemipentahydrate) salt.

The hemipentahydrate salt can be heated between 100-150 degrees C. for 1-4 hours to produce the hemihydrate.

The hemihydrate salt can be heated from 150-250 degrees C. for 1-4 hours to produce the anhydrous salt.

All of the above crystalline forms can be distinguished by their water content.

SUPPORTING EXAMPLE III

Preparation of 4-Amino-1-Hydroxy-Butylidene-1,1-Bisphosphonic Acid Monosodium Salt Anhydrate

To a suspension of 4-amino-1-hydroxy-1,1-diphosphonic acid (4.02 g) in 150 ml of distilled water was added with stirring aqueous sodium hydroxide (0.5N) until the pH of the soution was 4.40. The stirred solution was triturated with 200 ml ethanol (absolute) to give a suspension of a fine white solid which was chilled at 5 degrees C. overnight. The obtained solid was collected by vacuum filtration, air dried, and then dried *in vacuo* at 100 degrees C. at 0.2 torr for 18 hours over P_2O_5 to yield 3.38 g, (91%) yield of the titled compound. A sample was submitted for CHN analysis;

For $C_4H_{12}NO_7P_2Na$:

Anal.: C, 17.72; H, 4.46; N, 5.16

Found: C, 17.56; H, 4.67; N, 5.15

Melting Point of the solid was 244-245 degrees C.(d.)

The obtained titled salt displays a unique X-ray diffraction pattern.

Solubility of the anhydrous monosodium salt in water is about 300 mg/ml as compared to the free acid which is 8 mg/ml. However, above 40mg/ml, the trihydrate precipitates out of the aqueous solution.

The solution pH of the monosodium salt at 40 mg/ml. is 4.4, as compared to the free acid which is pH 2.2 at 8 mg/ml.

The water adsorption by the anhydrous salt at lower humidities is quite slow.

The following Examples are given to illustrate the carrying out of the invention as contemplated by the inventors and should not be construed as being limitations on the scope and spirit of the invention.

EXAMPLE 1

The following are examples of Palacos™R with Gentamicin base cement, commercially available, including new formulations with bisphosphonates, e.g., alendronate and calcium alendronate. Palacos is a registered trademark of Heraeus Kulzer GmbH Wehrheim, Germany, under license to Schering Plough, Suffolk, England.

Part A (Polymer Powder)

Sterilized polymer packet containing:

Ingredient	Grams
Methyl methacrylate - methyl acrylate copolymer	33.80
Benzoyl peroxide	0.20
Zirconium dioxide	6.00
Chlorophyll	0.001
Gentamicin Sulfate	0.5

Part B (Monomer)

Sterilized ampoule (20ml) containing:

Ingredient	Grams
Methyl methacrylate (stabilized with hydroquinone)	18.40
N,N-Dimethyl-p-toluidine	0.40
Chlorophyll	0.0004

Part B is added to Part A under sterile conditions with simple mixing and 1.186 grams (2 weight percent based on the weight of the cement composition prior to adding the bisphosphonate) of 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium trihydrate (alendronate) is added during the mixing step to achieve a uniform cement mixture containing:

Ingredient	Grams
Methyl methacrylate - methyl acrylate copolymer	52.2
Alendronate	1.186
Benzoyl peroxide	0.20
Zirconium dioxide	6.00
Chlorophyll	0.0014
Gentamicin Sulfate	0.5
N,N-Dimethyl-p-toluidine	0.40
Total	59.3

Similarly, 1.186 grams of a bisphosphonate selected from clodronate, tiludronate, YM 175, ibandronate, etidronate, risedronate, piridronate, pamidronate, 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monocalcium salt [(4-amino-1-hydroxybutylidene)-1,1-bisphosphonic acid]monocalcium salt, (ABP)Ca; di[(4-amino-1-hydroxybutylidene)-1,1-bisphosphonic acid]monocalcium salt, $(ABP)_2Ca$; and tri[(4-amino-1-hydroxybutylidene)-1,1-bisphosphonic acid]tetracalcium salt, $(ABP)_3Ca_4$, or mixture thereof being 2 weight percent of the cement composition, can also be used to produce separate cement formulations.

Further, different amounts of bisphosphonate can be used, for example, to achieve 0.005 to 10 weight percentages of the bone resorption inhibitor in the cement composition.

EXAMPLE 2

1. Alendronate Effects on Bone Formation and Resorbability of Bone Formed During Alendronate Treatment

Bisphosphonate drugs which prevent bone loss and/or add back lost bone can be evaluated in the ovariectomized rat. This animal model is well established in the art (see, for example, Wronski, *et al.*, (1985) "Calcif. Tissue Int." *37*:324-328; Kimmel, *et al.*, (1990) "Calcif. Tissue Int." *46*:101-110; and Durbridge, *et al.*, (1990) "Calcif. Tissue Int." *47*:383-387; these references are hereby

incorporated in their entirety). Wronski, *et al.*, ((1985) "Calcif. Tissue Int." *43*:179-183)) describe the association of bone loss and bone turnover in the ovariectomized rat. The bisphosphonate salts applicable in the instant invention are active in this assay.

2. Alendronate Effects on Osteolysis and Localized Inflammation in a Bone Cement

Following rat tibial marrow aspiration, according to the procedure described in *J. Bone Min. Research*, Vol. 8, No. 3, pp. 379-388 (1993) by L.J. Suva *et al.*, a quantity, 10-100 milligrams of polymethyl-methacrylate (PMMA) particles of about 5-10 microns average diameter, which can be derived from the grinding of a PMMA block, are introduced into the rat tibial medullary cavity and the bone sealed using conventional bone wax. This serves as the control.

The opposite side of the rat tibia is treated at about the same time and in the same manner except that the PMMA contains up to about 2 percent by weight of alendronate, either as the calcium or sodium salt, or other pharmaceutically acceptable salt. The alendronate salt is incorporated into the PMMA by simple mixing prior to polymerization until a uniform mixture is achieved.

After 4-8 weeks, the animal is sacrificed, and the tibiae are examined histologically and compared.

It is seen that the tibial medullary cavity containing PMMA particles without alendronate is expanded. This is evidence of localized inflammation and osteolysis.

By contrast, the tibia containing the alendronate exhibits no substantial localized inflammation or osteolysis, but instead, exhibits new bone formation in the region of the PMMA particles.

Therefore, the alendronate-containing PMMA prevents PMMA particle induced osteolysis and localized inflammation.

This is consistent with the method of administering a bisphosphonate-containing cement, e.g., alendronate, to a patient's periprosthetic bone area to prevent bone resorption and aseptic

loosening at the site of the medical implant device. The slowing of the rate of bone resorption, but not its complete inhibition, is predicted to be associated with an improvement in the local bone balance in the periprosthetic bone which will provide greater integrity to the overall bone and prosthesis structure.

WHAT IS CLAIMED IS:

1. A bone implant cement comprising a pharmaceutically acceptable polymeric carrier and an effective amount of a bisphosphonate bone resorption inhibitor.

2. The cement of Claim 1 wherein said bisphosphonate bone resorption inhibitor is selected from the group consisting of: sodium, potassium, calcium, magnesium and barium salts of alendronate, clodronate, tiludronate, YM 175, ibandronate, risedronate, piridronate, pamidronate, or mixtures thereof.

3. The cement of Claim 1 wherein said bisphosphonate bone resorption inhibitor is sodium alendronate.

4. The cement of Claim 1 wherein said bisphosphonate bone resorption inhibitor is calcium alendronate.

5. The cement of Claim 4 wherein said calcium alendronate is selected from the group consisting of: di[(3-amino-1-hydroxypropylidene)-1,1-bisphosphonic acid]tricalcium; [(4-amino-1-hydroxybutylidene)-1,1-bisphosphonic acid]monocalcium salt; di[(4-amino-1-hydroxybutylidene)-1,1-bisphosphonic acid]monocalcium salt; and tri[(4-amino-1-hydroxybutylidene)-1,1-bisphosphonic acid]tetra-calcium salt.

6. The cement of Claim 5 wherein said calcium salt of alendronate is [(4-amino-1-hydroxybutylidene)-1,1-bisphosphonic acid]monocalcium salt.

7. The cement of Claim 1 wherein said polymeric carrier is a polymethacrylate, polymethylmethacrylate, copolymer thereof, or copolymer with polyalkylmethylmethacrylate.

8. The cement of Claim 7 wherein said polymeric carrier is selected from the group consisting of: polymethyl-methacrylate, polyethylmethacrylate, polymethylmethacrylate-polymethacrylate copolymer, polymethacrylate, copolymer of methylmethacrylate/n-decylmethacrylate/isobornylmethacrylate.

9. The cement of Claim 8 wherein said polymeric carrier is polymethylmethacrylate.

10. The cement of Claim 1 wherein said bisphosphonate salt is present in about 0.005 to 10 weight percent of the total cement composition.

11 The cement of Claim 1 wherein said bisphosphonate salt is present in about 0.1 to 2 weight percent of the total cement composition.

12. The cement of Claim 1 wherein said bone resorption inhibitor is a calcium salt of alendronate and said polymeric carrier is polymethylmethacrylate.

13. The cement of Claim 1 wherein said bone resorption inhibitor is alendronate and said polymeric carrier is polymethyl-methacrylate.

14. The cement of Claim 1 further containing methyl methacrylate monomer.

15. The cement of Claim 1 wherein said polymethyl-methacrylate is fully cured.

16. A method of preventing failure of a joint prosthesis implanted into a bone cavity in the presence of an orthopedic bone cement in a patient comprising the steps of:

(a) adding a bisphosphonate to the orthopedic bone cement;

(b) adding the cement from step (a) to the bone cavity;

(c) implanting the joint prosthesis into the bone cavity.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/08515

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61F 2/28; A61K 6/08
US CL :523/116; 623/16

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 623/16; 523/116

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

NONE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US, A, 5,334,626 (LIN) 02 August 1994, see column 5 lines 47-30, and column 4 line 12.	1-16
Y	US, A, 5,409,911 (TYLER, ET AL.) 25 April 1995, see Abstract.	1-16
Y, P	US, A, 5,488,041 (BARBIER ET AL.) 30 January 1996, see columns 1 and 2.	2, 3
Y	US, A, 5,356,887 (BRENNER ET AL.) 18 October 1994, see entire document.	4-6, 12, 13
Y	US, A, 5,116,375 (HOFMANN) 26 May 1992, see column 1 lines 25-27.	14

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 AUGUST 1996	16 SEP 1996
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3590	Authorized officer Diane L. Smith for JOHN M. BLACK Telephone No. (703) 305-7341

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